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Cardiopulmonary and arterial baroreceptor unloading during passive hyperthermia does not contribute to hyperthermia-induced hyperventilation

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Abstract

This study tested the hypothesis that baroreceptor unloading during passive hyperthermia contributes to increases in ventilation and decreases in end-tidal partial pressure of carbon dioxide ($P_{\mathrm{ET,\ CO_2}}$) during that exposure. Two protocols were performed, in which healthy subjects underwent passive hyperthermia (increasing intestinal temperature by ~1.8°C) to cause a sustained increase in ventilation and reduction in $P_{\mathrm{ET,\ CO_2}}$. Upon attaining hyperthermic hyperventilation, in protocol 1 (n = 10; three females) a bolus (19 ± 2 ml kg^{-1}) of warm (~38°C) isotonic saline was rapidly (5–10 min) infused intravenously to restore reductions in central venous pressure, whereas in protocol 2 (n = 11; five females) phenylephrine was infused intravenously (60–120 μg min^{-1}) to return mean arterial pressure to normothermic levels. In protocol 1, hyperthermia increased ventilation (by 2.2 ± 1.7 l min^{-1}, P < 0.01), while reducing $P_{\mathrm{ET,\ CO_2}}$ (by 4 ± 3 mmHg, P = 0.04) and central venous pressure (by 5 ± 1 mmHg, P <0.01). Saline infusion increased central venous pressure by 5 ± 1 mmHg (P < 0.01), restoring it to normothermic values, but did not change ventilation or $P_{\mathrm{ET,\ CO_2}}$ (P > 0.05). In protocol 2, hyperthermia increased ventilation (by 5.0 ± 2.7l min^{-1}, P <0.01) and reduced $P_{\mathrm{ET\ ,\ CO_2}}$ (by 5 ± 2 mmHg, P < 0.01) and mean arterial pressure (by 9 ± 7 mmHg, P <0.01). Phenylephrine infusion increased mean arterial pressure by 12 ± 3 mmHg (P < 0.01), restoring it to normothermic values, but did not change ventilation or $P_{\mathrm{ET,\ CO_2}}$ (P > 0.05). The absence of a reduction in ventilation upon reloading the cardiopulmonary and arterial

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Competing interests

None declared.

Author contributions

All authors contributed to the conception and design of the experiment, collection, analysis and interpretation of data and writing the manuscript. All authors read and approved the final manuscript.

baroreceptors to pre-hyperthermic levels indicates that baroreceptor unloading with hyperthermia is unlikely to contribute to hyperthermic hyperventilation in humans.

Introduction

Hyperthermic hyperventilation is well documented in humans and is associated with high skin and body core temperatures (T_{core}, in excess of +1.0°C; Cabanac & White, 1995; Fujii *et al.* 2008*b*). Given the relatively minor contribution of respiratory heat loss with respect to human heat balance, the mechanism(s) and/or the physiological relevance of hyperthermic hyperventialtion in humans are unclear. Previous mechanisms proposed to contribute to this response in humans include selective brain cooling (White, 2006), heightened chemoreceptor sensitivity (Fujii *et al.* 2008*a*) and increases in cutaneous vasodilatation (Hayashi *et al.* 2009). However, the effectiveness of respiratory heat dissipation in the absence of cooling devices (i.e. face fanning or nasopharyngeal coolant spray) challenges the validity of selective brain cooling (Nybo & Secher, 2011). Furthermore, chemoreceptors contribute little to hyperthermic hyperventilation (Fujii *et al.* 2008*a*), and enhanced skin vasodilatation via heat acclimatization does not alleviate hyperthermic hyperventilation (Fujii *et al.* 2012). Rapid skin surface cooling (excluding the head) restores $P_{\mathrm{ET,\ CO_2}}$ and presumably reverses hyperventilation during severe hyperthermia (Lucas *et al.* 2010). However, it is unknown whether this is due to a cold-induced pressor response and subsequent loading of the baroreceptors (Wilson *et al.* 2007*a*).

Hyperventilation is also triggered by hypotension in normothermic (Convertino *et al.* 2009; Thomas *et al.* 2009; Stewart *et al.* 2011) and hyperthermic conditions (Pearson *et al.* 2013). For example, pharmacological unloading and loading of the baroreceptors, via decreasing (by ~18 mmHg) and increasing arterial blood pressure (by ~8 mmHg), causes ventilation to increase (by 9.7 ± 2.4 l $\mathrm{min^{-1}}$) and decrease (by 5.1 ± 1.1 l $\mathrm{min^{-1}}$), respectively (Stewart *et al.* 2011). The physiological significance of such a response may be the capacity of the respiratory pump to increase venous return and cardiac filling; that is, increasing respiration and subsequent generation of a more negative intrathoracic pressure aids cardiac filling and increases cardiac output as well as arterial and central venous pressures (CVP; Kilburn & Sieker, 1960; Moreno *et al.* 1967; Conway, 1975). Therefore, increased respiratory pump activation may be a protective mechanism triggered to optimize cardiac filling in conditions of central hypovolaemic hypotension (Convertino *et al.* 2009).

Hyperthermia and associated heat-dissipation mechanisms also reduce cardiac filling pressure, central blood volume and mean arterial pressure (MAP), consequently unloading the cardiopulmonary and arterial baroreceptors (Rowell *et al.* 1969; Wilson *et al.* 2007*b*; Ganio *et al.* 2011). Thus, prolonged hyperthermia-related hypotension and the corresponding unloading of baroreceptors may contribute to hyperthermic hyperventilation. However, the influence of baroreceptor unloading on hyperthermic hyperventilation has not been examined. In the present study, therefore, we tested the following hypothesis: cardiopulmonary baroreceptor unloading and arterial baroreceptor unloading during passive hyperthermia contribute to increases in ventilation and decreases in end-tidal partial pressure of carbon dioxide $(P_{\mathrm{ET,\ CO_2}})$ during that exposure.

Methods

Two protocols were undertaken for this study. For protocol 1, 10 subjects participated (three females; age, 29 ± 5 years; height, 177 ± 10 cm; and weight, 75.5 ± 12.2 kg). For protocol 2, 11 subjects participated (five females; age, 26 ± 5 years; height, 178 ± 12 cm; and weight, 71.3 ± 14.9 kg). Subjects were not taking medications, were free of any known cardiovascular, metabolic or neurological diseases and were non-smokers. As only within-subject comparisons were performed (see '*Data collection and statistics*' section), menstrual cycle phase was recorded but not controlled for in female subjects. Subjects were asked to abstain from exercise and alcohol for 24 h before testing, as well as caffeine for 12 h. Each subject was fully informed of the experimental procedures and possible risks before giving informed, written consent, but subjects were not informed of the proposed hypothesis. Both protocols and the informed consent were approved by the Institutional Review Boards at the University of Texas Southwestern Medical Center at Dallas and Texas Health Presbyterian Hospital of Dallas, and all procedures conformed to the standards set by the *Declaration of Helsinki*.

Instrumentation

For both protocols, subjects were dressed in a long-sleeved and long-legged, two-piece, tube-lined perfusion suit (Med-Eng, Ottawa, ON, Canada), enabling the control of skin temperature and T_{core} via the temperature of the water perfusing the suit. Measurements of T_{core} were derived from a telemetry temperature pill swallowed ~2 h before the onset of data collection (HQ Inc., Palmetto, FL, USA). Whole-body mean skin temperature was measured from the weighted average of six thermocouples attached to the skin with porous adhesive tape on the calf (11%), thigh (14%), abdomen (14%), chest (22%), lower back (19%) and upper back (20%; Taylor *et al.* 1989). Expired air was sampled via a facemask attached to a two-way valve (Hans Rudolf, Inc., Shawnee, KS, USA). Ventilatory parameters (ventilation, tidal volume and breathing rate) were measured (body temperature and pressure saturated) using an automated gas analysis system (TrueOne 2400; Parvo-Medics, Sandy, UT, USA), with values recorded over 15 s epochs. The $P_{\mathrm{ET,\ CO_2}}$ was sampled from the mask and measured using a capnograph (9004 Capnocheck® Plus; Smiths Medical International Ltd, Watford, UK). Heart rate was collected from an ECG signal (Agilent, Munich, Germany) interfaced with a cardiotachometer (1000 Hz sampling rate; CWE, Ardmore, PA, USA). Beat-to-beat arterial blood pressure was measured and reconstructed to give brachial artery pressure via finger-cuff photoplethysmography (Finometer Pro; FMS, Amsterdam, The Netherlands or NexFin HD; BMEYE BV, Amsterdam, The Netherlands).

Experimental protocol 1

This protocol was performed to determine whether reloading primarily the cardiopulmonary baroreceptors and increasing CVP would attenuate hyperthermic hyperventilation. In eight of the 10 subjects, a peripherally inserted central venous catheter was advanced into the superior vena cava via the basilic vein. Positioning of the central venous catheter was confirmed by the following observations: (i) the distance that the catheter was advanced relative to the subject's height; (ii) adequate pressure waveforms; and (iii) an appropriate rapid rise and fall in pressure during a Valsalva and Müller manoeuvre, respectively. The

central venous catheter was connected to a pressure transducer and zeroed at the position of the mid-axillary line. This catheter was used for continuous measurement of CVP.

Following instrumentation, subjects rested in the supine position for a minimum of 30 min, while water at 34°C circulated through the suit. After ~20 min of wearing the facemask (ensuring steady-state ventilatory responses), normothermic baseline thermal, haemodynamic and respiratory measures were obtained. To minimize participant's discomfort, the facemask was removed after these normothermic measurements. Subjects were then passively heated by circulating water at ~49°C through the suit. Between 10 and 15 min into the passive heating phase, the facemask was re-attached, and ventilation and $P_{\mathrm{ET,\ CO_2}}$ were monitored for at least 20 min before hyperthermia measurements were taken (42 ± 13 and 33 ± 9 min in protocols 1 and 2, respectively). After T_{core} had increased (1.9 ± 0.5°C) and there was a consistent increase in ventilation, associated with a ~5 mmHg reduction in $P_{\mathrm{ET,\ CO_2}}$, 19 ± 2 ml kg^{-1} warmed (~38°C) isotonic saline was rapidly administered over 6.9 ± 2.1 min through a separate catheter placed in an antecubital vein, as this rate and volume are sufficient to return CVP to pre-hyperthermic pressures (Crandall *et al.* 1999). The duration of the saline infusion differed between subjects (range, 5 – 10 min). After the infusion and subsequent data collection, skin surface cooling was performed by circulating water at ~20°C through the water-perfusion suit for 10 min. This method of cooling rapidly decreases the mean skin temperature with little initial effect on T_{core} (see Results).

Experimental protocol 2

This protocol was performed to determine whether reloading primarily the arterial baroreceptors and increasing MAP would attenuate hyperthermic hyperventilation. This protocol was almost identical to that outlined in the previous subsection; however, rather than administering warm saline, phenylephrine (PE; 60–120 μg min^{-1}) was titrated intravenously for 5 min to increase MAP by 12 ± 3 mmHg. In protocol 2, participants lay supine with their lower legs off the end of the bed and their feet on a footstool, so that their knee angle was ~73 deg. This was done to aid venous pooling and augment hyperthermia-related reductions in MAP. Also, mean skin temperature was gradually returned to pre-hyperthermic stress levels 5 min after the PE infusion ended in order to avoid a potential hypertensive event that would otherwise occur with whole-body cooling in combination with the administered PE.

Data collection and statistics

Data were acquired continuously at 50 Hz throughout the experiment (Biopac, Santa Barbara, CA, USA) and were reduced into the following 1 min periods: immediately before whole-body heating (normothermia); immediately before rapid saline infusion or PE administration (hyperthermia); and during rapid saline and PE infusions. The duration of rapid saline infusion differed between subjects; therefore, the final 5 min of the infusion are presented. All data were statistically analysed using one-way repeated-measures ANOVA with the repeated factor of time (normothermia, hyperthermia and the final 5 min of rapid saline or PE infusions), followed by Tukey-corrected *post hoc* tests when significant differences were identified. Additionally for protocol 1, the fifth minute of skin surface

cooling after the heat stress was analysed and compared using a one-way repeated-measures ANOVA with normothermia, hyperthermia and the final minute of rapid saline infusion. A skin surface cooling time point was not included in protocol 2 analysis on account of the gradual skin surface cooling employed. A linear regression analysis was performed to characterize further the relationship between changes in ventilation and CVP or MAP during rapid saline, skin surface cooling or PE infusion, respectively. Each subject's change scores for ventilation, CVP ($n = 8$) and MAP ($n = 11$) were calculated from the difference between 1 mi hyperthermic baseline and rapid saline infusion, skin surface cooling or PE infusion periods. Data were analysed using GraphPad Prism (version 6; GraphPad Software, Inc., La Jolla, CA, USA) with *a priori* statistical significance set at $P \leq 0.05$. All data are reported as mean values ± SD.

Results

Protocol 1

Passive hyperthermia increased T_{core} (by 1.9 ± 0.5°C, $P < 0.01$) and mean skin temperature (by 4.7 ± 0.7°C, $P < 0.01$) and decreased CVP (by 5 ± 1 mmHg, $P < 0.01$; Table 1 and Fig. 1). This was accompanied by an increase in ventilation (by 2.2 ± 1.7 l min^{-1}, $P < 0.01$) and tidal volume (by 0.4 ± 0.3 litres, $P = 0.04$), together with a reduction in $P_{ET,\ CO_2}$ (by 4 ± 3 mmHg, $P = 0.04$; Fig. 2) when compared with normothermia. Rapid infusion of 19 ± 2 ml kg^{-1} saline increased CVP (by 5 ± 1 mmHg, $P < 0.01$) but did not change ventilation ($P = 0.70$) or $P_{ET,\ CO_2}$ ($P = 0.98$) relative to pre-infusion hyperthermic values. The T_{core} and mean skin temperature values were not different between hyperthermia and rapid infusion ($P > 0.05$).

Skin surface cooling after the heat stress lowered mean skin temperature (by 4.7 ± 1.5°C, $P < 0.01$) but did not change T_{core} ($P = 0.99$) from rapid infusion values. With skin surface cooling, CVP remained 5 ± 1 mmHg higher ($P < 0.01$) than pre-infusion hyperthermic values. Notably, skin surface cooling returned tidal volume ($P = 0.98$) and ventilation ($P = 0.52$) to values similar to those in normothermia, but $P_{ET\ ,\ CO_2}$ remained slightly depressed (by 4 ± 2 mmHg, $P = 0.01$; Fig. 2. There was no association between increasing CVP and ventilation with either rapid saline infusion ($r^2 = 0.06$, $P = 0.55$; Fig. 3*A*) or skin surface cooling ($r^2 = 0.05$, $P = 0.61$; Fig. 3*B*).

Protocol 2

Passive hyperthermia increased T_{core} (by 1.8 ± 0.5°C, $P < 0.01$), increased mean skin temperature (by 6.0 ± 0.7°C, $P < 0.01$) and decreased MAP (by 9 ± 7 mmHg, $P < 0.01$; Table 2 and Fig. 4). This was accompanied by an increase in ventilation (by 5.0 ± 2.7 l min^{-1}, $P < 0.01$) and a reduction in $P_{ET,\ CO_2}$ (by 5 ± 2 mmHg, $P < 0.01$). Relative to pre-infusion hyperthermia, PE elevated MAP (by 12 ± 3 mmHg, $P < 0.01$), but did not change ventilation ($P = 0.66$) or $P_{ET,\ CO_2}$ ($P = 0.66$; Fig. 5). The T_{core} from hyperthermic values during the PE infusion ($P = 0.93$). There was a weak association between PE-induced increases in MAP and changes in ventilation ($r^2 = 0.33$, $P = 0.07$; Fig. 6).

Discussion

This is the first study to examine whether cardiopulmonary or arterial baroreceptor unloading contributes to hyperthermic hyperventilation. The novel findings from this study are that hyperthermic hyperventilation is not mitigated by (i) expanding central blood volume and reloading the cardiopulmonary baroreceptors via rapid saline infusion, and (ii) reloading the arterial baroreceptors via PE administration. The absence of a reduction in ventilation during these perturbations indicates that cardiopulmonary or arterial baroreceptor unloading coincident with hyperthermia is unlikely to contribute to hyperthermic hyperventilation.

In the present study, participants' hyperthermic hyperventilatory response following baroreceptor reloading varied in both protocols 1 and 2. In protocol 1, ventilation decreased to some extent in four of the eight participants with rapid infusion (Fig. 3*A*). Likewise, in protocol 2, ventilation decreased in seven of the 11 participants with PE infusion (Fig. 6). Thus, it may be that reloading the cardiopulmonary or the arterial baroreceptors attenuates hyperthermic hyperventilation in some individuals. Nevertheless, this interparticipant variation may also be due to various behavioural ventilatory influences (i.e. modulators largely unaffected by the homeostatic regulation of arterial blood gas tension; Shea, 1996). Interparticipant variation for the onset of hyperthermic hyperventilation has been reported previously (Fujii *et al.* 2008*b*). There also appear to be intraparticipant differences according to the type of hyperthermic stimulus, with passive hyperthermia inducing a greater hyperventilatory response in comparison to exercise (Fujii *et al.* 2008*b*). Thus, behavioural ventilatory control elements may prevail over hyperthermic physiological ventilator drivers in some individuals. Interestingly, PE-induced arterial baroreceptor reloading tended to be associated with a decrease in ventilation ($r^2 = 0.33$). It has previously been shown that a bolus PE infusion decreases ventilation in normothermic conditions (Stewart *et al.* 2011). Thus, the presence of a ventilatory baroreflex may remain while an individual is hyperthermic; however, it remains unlikely that cardiopulmonary or arterial baroreceptor unloading contributes to hyperthermic hyperventilation in general.

Notably, rapid skin surface cooling restores $P_{\mathrm{ET,\ CO_2}}$ during severe hyperthermia (T_{core} increased by 2°C) combined with lower body negative pressure (15 mmHg; Lucas *et al.* 2010). Likewise, in the present study, skin surface cooling reduced tidal volume and ventilation from hyperthermic and rapid infusion values (Table 1). Rapid skin cooling elicits a pressor response whereby peripheral and visceral arteries constrict and central venous and right and left ventricular filling pressures increase (Wilson *et al.* 2007*a*,*b*). However, findings from the present study indicate that this pressor response is unlikely to contribute to reductions in hyperthermic hyperventilation with rapid skin cooling, as baroreceptor reloading alone did not attenuate hyperthermic hyperventilation. Given that hyperthermic hyperventilation is associated with high T_{core} and skin temperatures (Cabanac & White, 1995; Fujii *et al.* 2008*b*), it is possible that high thermoafferent activity from both the core and the skin may drive hyperthermic hyperventilation. Animal studies have shown that stimulation of hypothalamic thermosensitive neurons increases neural activity of the ventral respiratory group and, consequently, ventilation (Boden *et al.* 2000; Tryba & Ramirez, 2003). If this is the case, presumably rapid skin cooling reduces hyperthermic

thermoafferent activity and, subsequently, some of the stimulus for hyperventilation. However, such a relationship between thermoafferent neural activity and ventilation has not been examined directly in humans. Alternatively, subjective relief from high skin temperatures with rapid skin cooling may also underlie reductions in hyperthermic hyperventilation. Hyperventilation can be associated with highly arousing negative emotions (Boiten *et al.* 1994), such as might be elicited from the great thermal discomfort accompanying elevated skin and body core temperatures. Thus, hyperthermic hyperventilation may not serve a physiological purpose, but rather is a response to a state of considerable thermal discomfort, anxiety and/or arousal. If this is the case, the relatively high cutaneous contribution to subjective thermal comfort may explain, in part, why rapid skin surface cooling reduces hyperventilation while T_{core} remains elevated (Frank *et al.* 1999). It may also explain the interparticipant variation in hyperthermic hyperventilation, as individuals with more experience and/or resilience (both physiologically and psychologically) to hyperthermia (for example, owing to habitual exercise in warm environments) may be better able to manage thermal discomfort and any resulting hyperthermic hyperventilation. Thus, perhaps hyperthermic hyperventilation indicates when an individual is reaching their psychophysiological hyperthermic limit.

Technological considerations

Central venous pressure was measured in eight of the 10 subjects. As there is no reason to believe that CVP would respond differently during rapid saline infusion in the two subjects who refused the CVP catheter, we deemed it justifiable to include their data within the analyses.

In both protocols, rapid saline infusion and administration of PE were initiated when T_{core} was very high (39.0 and 38.9°C, respectively). It is possible that such high T_{core} and accompanying thermal discomfort dominated any potential baro-mediated ventilatory response. However, this magnitude of hyperthermia was necessary because hyperventilation was a prerequisite for testing our hypotheses. For the present study, we considered that a consistent increase in ventilation, associated with a ~5 mmHg reduction in $P_{\text{ET, CO}_2}$, would be indicative of hyperthermic hyperventilation. We anticipated that this degree of hyperthermic hyperventilation would occur at a T_{core} of 38–38.5°C based on previous studies (Cabanac & White, 1995; Fujii *et al.* 2008*b*). However, participants in the present study did not show a consistent hyperventilation until they reached a higher T_{core}, indicative of the intraparticipant variability of this response (Fujii *et al.* 2008*b*). A possible explanation for this observation may be the facemask familiarization used in the present protocol. Each subject wore the facemask for at least 20 min prior to normothermic and hyperthermic data collection, thus reducing the likelihood of ‘artificially’ triggering hyperventilation and affecting the T_{core} threshold for hyperthermic hyperventilation via application of the facemask.

Rapid skin surface cooling after heat stress increased $P_{\text{ET, CO}_2}$ by 2 mmHg, but that value remained below the normothermic baseline, whereas at similar T_{core} Lucas *et al.* (2010) found that $P_{\text{ET, CO}_2}$ increased by 7 mmHg with skin surface cooling. This difference is likely to be due to the differences in the water temperature perfusing the suit, with use of 15°C

water as opposed to the 20°C water in the present study, determining that a more modest cooling stimulus elicited a smaller reduction in hyperthermic hyperventilation. In the present study, this was designed to avoid overloading the central vascular space and unsafely increasing central venous and arterial pressure, given the volume-loaded state of these individuals following saline infusion. For the same reason, skin temperature was lowered slowly in protocol 2; hence, no skin surface cooling data are presented. This further highlights the impact of reducing skin temperature on ventilator responses.

Implications

Findings from the present study further highlight the importance of reducing high skin temperatures in hyperthermic individuals. Acute baroreceptor loading alone does not appear to circumvent hyperventilatory-induced hypocapnia, which affects cerebral perfusion owing to the cerebral vasoconstriction associated with reductions in arterial P_{CO_2} (Kety & Schmidt, 1948). However, this and previous studies indicate that lowering high skin temperatures in hyperthermic individuals attenuates hyperventilation (Lucas *et al.* 2010). This has ramifications for avoiding syncope and maintaining consciousness during a hyperthermic, hypotensive challenge.

Also, findings from the present study further support the intraparticipant variability associated with hyperthermic hyperventilation (Fujii *et al.* 2008*b*). This degree of variability coupled with a possible role of thermal discomfort in passive hyperthermic hyperventilation seem to indicate a psychophysical influence on hyperthermic hyperventilation. If this is the case, it may be that mental preparation or habituation, as has been observed in the cold (Croft *et al.* 2013), can affect an individual's hyperthermic hyperventilatory threshold, which perhaps explains the variability of this response reported in the literature. However, a psychophysical effect has not been formally established to date.

Conclusion

In the present study, rapid saline infusion and administration of PE successfully elevated CVP and MAP, respectively, ameliorating hyperthermia-related unloading of these baroreceptors. Despite this, ventilation and $P_{\mathrm{ET,\ CO}_2}$ did not change from pre-infusion hyperthermic values. These findings strongly indicate that hyperthermic hyperventilation is not affected by cardiopulmonary or arterial baroreceptor unloading coincident with hyperthermia.

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New Findings

- **What is the central question of this study?**

  Does baroreceptor unloading during passive hyperthermia contribute to increases in ventilation and decreases in end-tidal carbon dioxide during that exposure?

- **What is the main finding and its importance?**

  Hyperthermic hyperventilation is not mitigated by expanding central blood volume and reloading the cardiopulmonary baroreceptors via rapid saline infusion or by reloading the arterial baroreceptors via phenylephrine administration. The absence of a reduction in ventilation upon reloading the baroreceptors to pre-hyperthermic levels indicates that cardiopulmonary and arterial baroreceptor unloading with hyperthermia is unlikely to contribute to hyperthermic hyperventilation in humans.

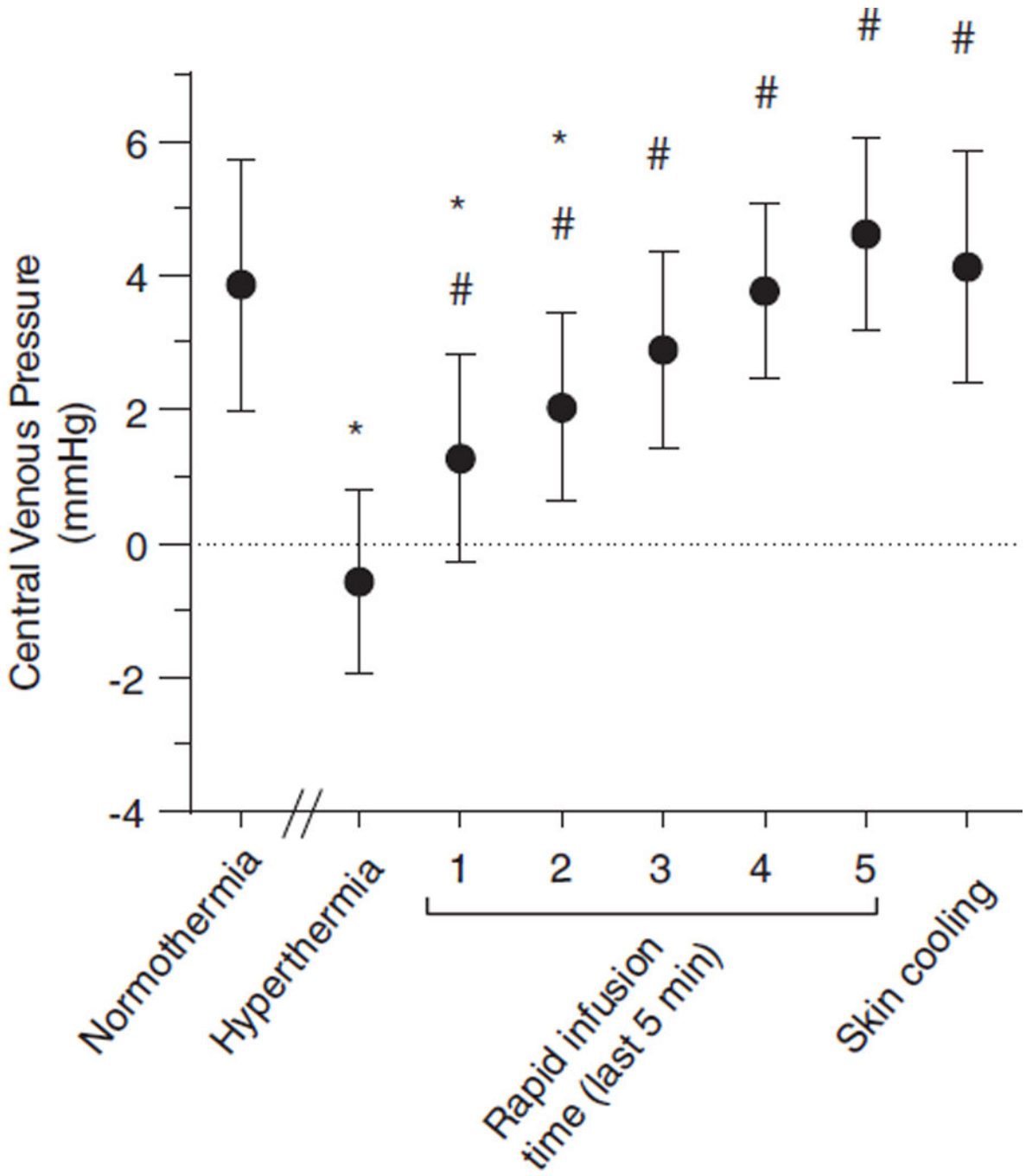

Figure 1. Central venous pressure (n = 8) immediately prior to whole-body passive hyperthermia (normothermia), during hyperthermia alone and throughout the final 5 min of rapid saline infusion while hyperthermic

*Significantly different from normothermia, $P < 0.05$; and #significantly different from hyperthermia, $P < 0.05$.

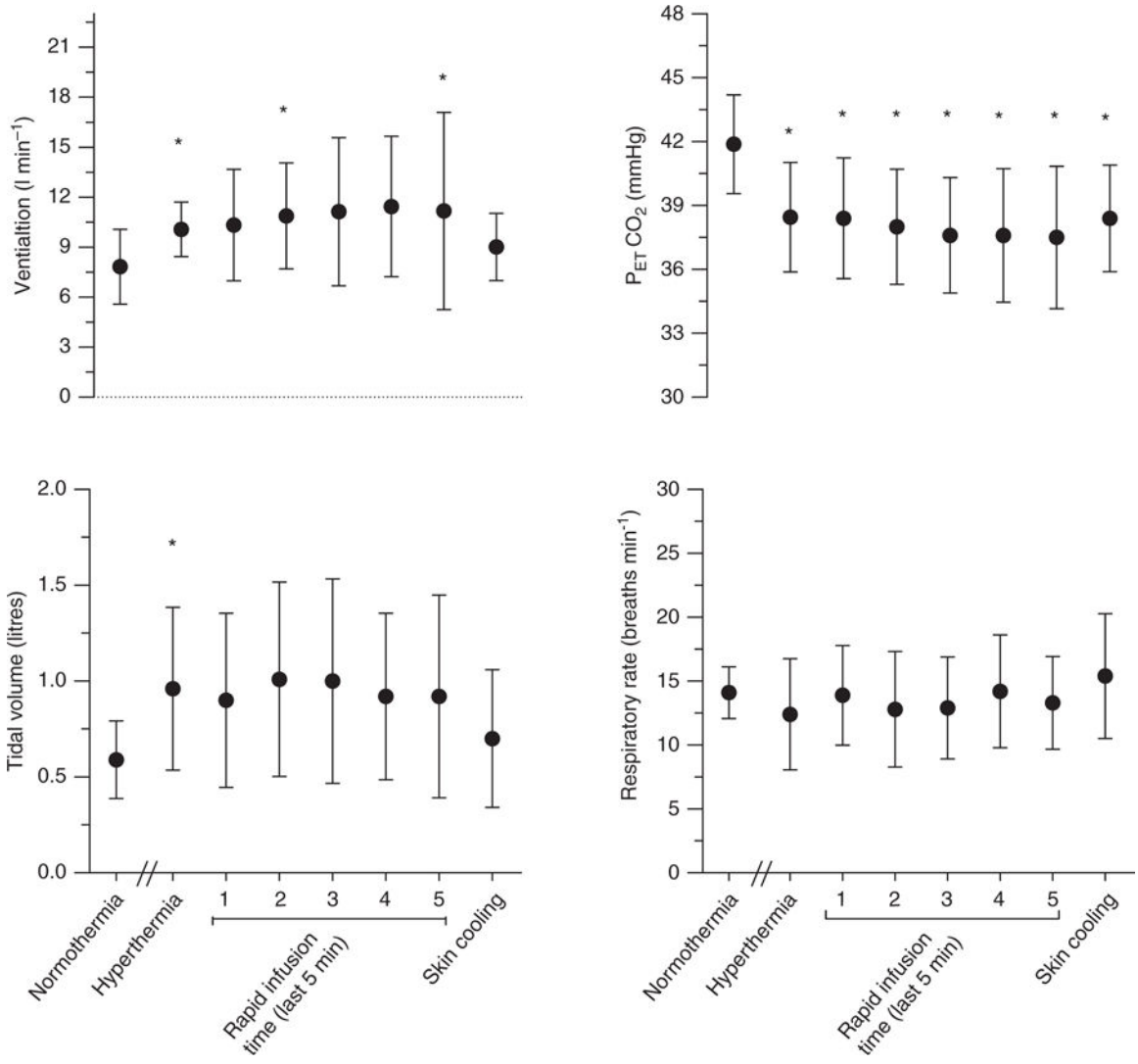

Figure 2. Respiratory responses immediately prior to whole-body passive hyperthermia (normothermia), during hyperthermia alone and throughout the final 5 min of rapid saline infusion while hyperthermic

*Significantly different from normothermia, $P < 0.05$.

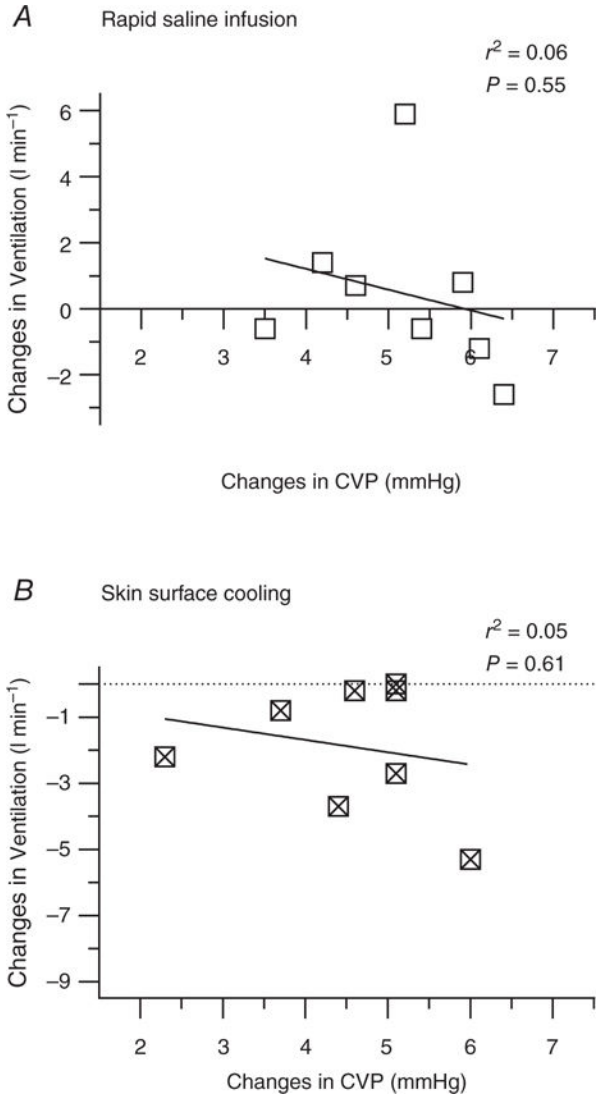

Figure 3. The relationships between changes in ventilation and central venous pressure (CVP) following rapid saline infusion (relative to hyperthermia; *A*) and following skin surface cooling (relative to hyperthermia; *B*)

Data are individual responses to rapid saline infusion (n = 8).

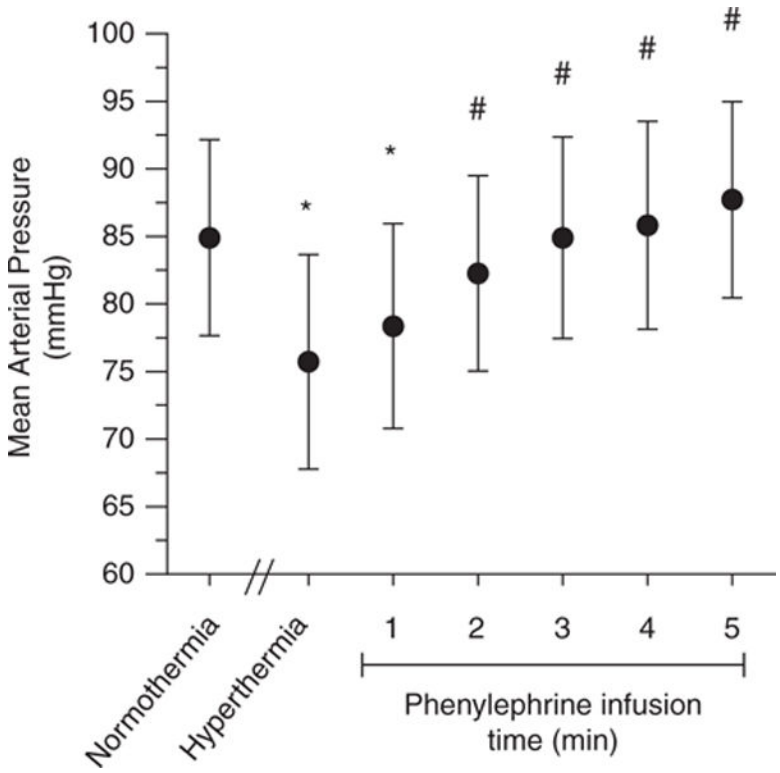

Figure 4. Mean arterial pressure immediately prior to whole-body passive hyperthermia (normothermia), during hyperthermia alone and throughout the first 5 min of phenylephrine infusion

*Significantly different from normothermia, $P < 0.05$; and #significantly different from hyperthermia, $P < 0.05$.

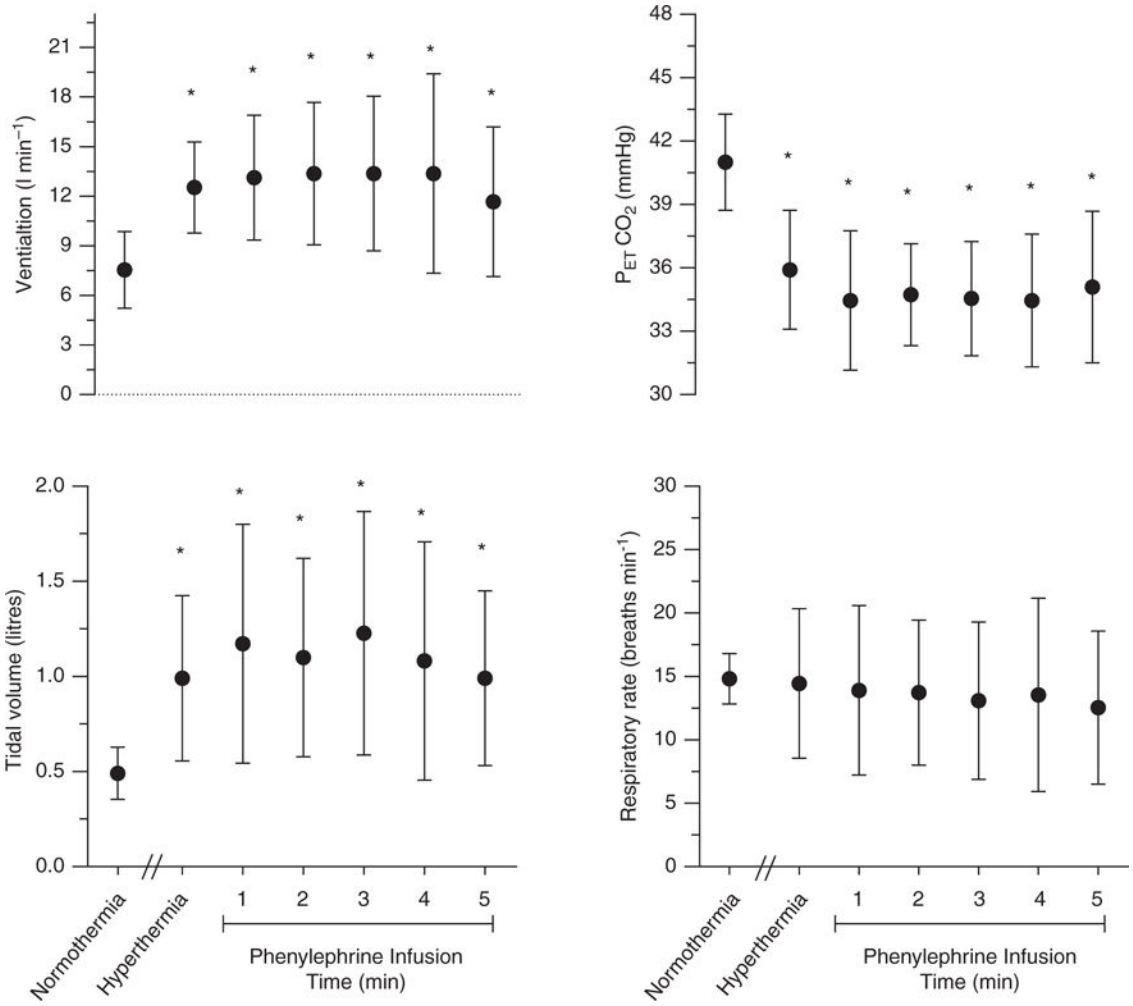

Figure 5. Respiratory responses immediately prior to whole-body passive hyperthermia (normothermia), during hyperthermia alone and throughout the first 5 min of phenylephrine infusion

*Significantly different from normothermia, $P < 0.05$.

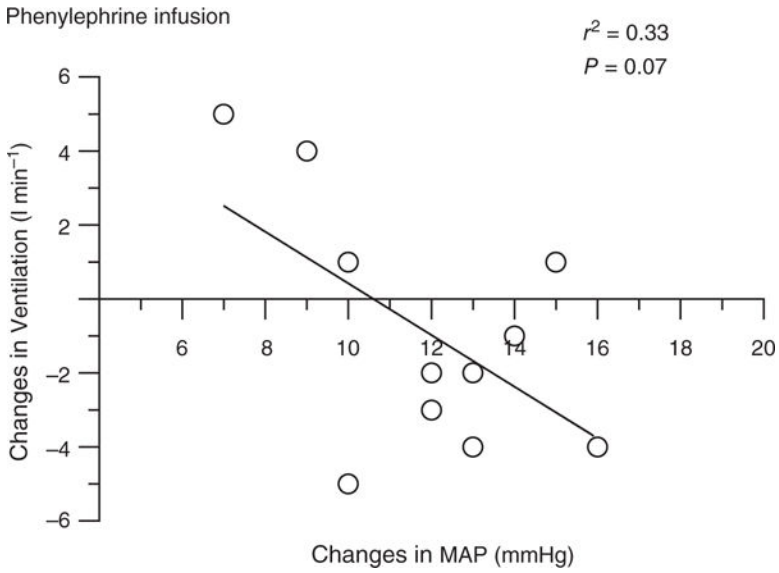

Figure 6. The relationships between changes in ventilation and Mean arterial pressure (MAP) following phenylephrine infusion (relative to hyperthermia)

Data are individual responses to PE infusion (n = 11).

Table 1

Thermal, haemodynamic and respiratory parameters during normothermia, hyperthermia, rapid saline infusion and skin surface cooling for protocol 1

Parameter	Normothermia	Hyperthermia	Rapid infusion	Skin cooling
Body core temperature (°C)	37.0 ± 0.3	38.9 ± 0.4 *	39.0 ± 0.5 *	39.0 ± 0.5 *
Mean skin temperature (°C)	34.7 ± 0.2	39.4 ± 0.8 *	39.2 ± 0.8 *	34.5 ± 0.9 †‡
Mean arterial pressure (mmHg)	82 ± 8	79 ± 11	74 ± 8 *	74 ± 8 *
Heart rate (beats min^{-1})	59 ± 10	113 ± 17 *	112 ± 14 *	96 ± 13 *†‡

* Significantly different from normothermia $P < 0.05$;

† significantly different from hyperthermia, $P < 0.05$;

‡ significantly different from rapid infusion, $P < 0.05$. Values are 1 min means ± SD.

Table 2

Thermal and haemodynamic paramters during normothermia, hyperthermia and the fifth minute of phenylephrine infusion for protocol 2

Parameter	Normothermia	Hyperthermia	PE infusion
Body core temperature (°C)	36.9 ± 0.2	38.7 ± 0.4 *	38.9 ± 0.5 *
Mean skin temperature (°C)	33.9 ± 0.5	39.9 ± 0.5 *	39.8 ± 0.5 *
Heart rate (beats min^{-1})	56 ± 10	107 ± 16 *	95 ± 15 *†

*Significantly different from normothermia, $P < 0.05$;

†significantly different from hyperthermia, $P < 0.05$. Values are 1 min means ± SD.